Exhibit D

A randomised controlled trial with prolonged-release oral oxycodone and naloxone to prevent and reverse opioid-induced constipation

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ABSTRACT

Background: Opioid-induced constipation can have a major negative impact on patients' quality of life. This randomised, double-blinded study evaluated the analgesic efficacy of prolonged-release (PR) oral oxycodone when co-administered with PR oral naloxone, and its impact on opioid-induced constipation in patients with severe chronic pain. Another objective was to identify the optimal dose ratio of oxycodone and naloxone.

Methods: A total of 202 patients with chronic pain (mainly non-cancer related, 2.5% of patients had cancer-related pain) under stable oral oxycodone therapy (40, 60 or 80 mg/day) were randomised to receive 10, 20, 40 mg/day naloxone or placebo. After a 4-week maintenance phase, patients received oxycodone only for 2 weeks. Pain intensity was evaluated using a numerical analogue scale and bowel function was assessed using the bowel function index.

Results: No loss of analgesic efficacy with naloxone was observed. Mean pain intensity scores on randomisation were comparable for placebo, 10 mg, 20 mg and 40 mg naloxone dose, and remained unchanged during treatment. Bowel function improved with increasing naloxone dose. Naloxone 20 mg and 40 mg significantly improved bowel function at the end of the maintenance phase compared with placebo ($p < 0.05$). Overall, the combination was well tolerated, with no unexpected adverse events. There was a trend towards an increased incidence of diarrhoea with higher doses of naloxone. The 2:1 oxycodone/naloxone ratio was identified as the most suitable for further development.

Conclusion: Co-administration of PR oral naloxone and PR oral oxycodone is associated with a significant improvement in bowel function compared with PR oral oxycodone alone, with no reduction in the analgesic efficacy of oxycodone.

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1. Introduction

Oxycodone is a strong, semi-synthetic, well established opioid analgesic that has been in clinical use since 1917 for the treatment of severe pain (Kalso, 2005). Oxycodone is effective in severe chronic pain, whether nociceptive, cancer-related or neuropathic pain (Watson and Babul, 1998; Gimbel et al., 2003; Watson et al., 2003; Coluzzi and Mattia, 2005; Riley et al., 2008).

Like all opioids, oxycodone can be associated with the development of bowel dysfunction, which encompasses symptoms including bloating, abdominal spasm and cramps and constipation (Pappagallo, 2001). Constipation is the most frequently reported

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adverse effect in patients receiving chronic opioid therapy (Thorpe, 2001; Coluzzi and Mattia, 2005), and is mediated mainly through stimulation of opioid receptors in the gastrointestinal tract. Opioids reduce motility (propulsive peristalsis) and secretion (water and electrolytes) (DeLuca and Coupar, 1996). Fluid absorption is also increased due to the increase in transit time (Holzer, 2007). These local actions in the intestine lead to the development of constipation, which represents a significant clinical problem.

Opioid-induced constipation can be so severe that some patients opt to discontinue therapy; this results in analgesic undertreatment, severely impairing quality of life (Derby and Portenoy, 1998; Cherny et al., 2001; Kurz and Sessler, 2003; Wirz and Klaschik, 2005). In patients who remain on therapy, frequent opioid dose reductions limit efficacy. Tolerance to opioid-induced

constipation rarely develops (Swegle and Logemann, 2006). Furthermore, as opioids inhibit gastrointestinal transit at doses much lower than those needed to produce analgesia (Shook et al., 1987), this side effect cannot be managed by reducing opioid dose. A significant proportion of patients who receive opioids on a long-term basis require treatment with a laxative. In a survey of 76 patients treated with opioids for non-cancer related pain, 88% used at least one treatment for constipation, while 58% received two or more (Pappagallo, 2001). In a retrospective study of 206 patients undergoing opioid therapy in palliative care, constipation was treated prophylactically or therapeutically with laxatives in 74.3% of patients (Wirz and Klaschik, 2005). However, laxatives do not address the underlying pathological cause of opioid-induced constipation, and it therefore persists in many patients (Pappagallo, 2001; Kurz and Sessler, 2003). Consequently, an effective therapeutic strategy to manage opioid-induced constipation is to prevent, rather than to treat it (Kurz and Sessler, 2003).

Naloxone is a pure opioid receptor antagonist commonly used intravenously to reverse opioid overdose. Although relatively well absorbed after oral administration, it undergoes extensive first-pass metabolism (glucuronidation) (De Schepper et al., 2004). Following oral administration, naloxone has a low oral bioavailability of <2%. It undergoes extensive hepatic metabolism to form the partly active metabolite 6β-naloxol and glucuronides of naloxone and 6β-naloxol (Weinstein et al., 1971). Consequently, orally administered naloxone has dose-dependently negligible systemic bioavailability at the concentrations used in the present study – its central effects are none or minimal but it can exert a full, local inhibitory effect on opioid receptors in the intestine. The primary local effect of naloxone is at the local intestinal wall, presumably at the site of the opioid receptors in the myenteric plexus and other neural and endocrine cells in the intestine (Kreek et al., 1983; Culpepper-Morgan et al., 1992). The co-administration of naloxone and oxycodone could therefore provide full analgesia while preventing, or minimising, opioid-induced constipation.

This Phase II trial was conducted to assess the impact of orally administered PR naloxone on the analgesic efficacy of PR oxycodone and opioid-induced constipation in patients with severe chronic pain. The study also allowed the determination of the most appropriate dose ratio for a fixed, PR oxycodone/naloxone combination tablet.

2. Methods

2.1. Patients

This was a multicentre, prospective, placebo-controlled, randomised, double-blind, parallel-group Phase II trial conducted in 28 centres in Germany from May 2002 to April 2003. The study was conducted in accordance with the Declaration of Helsinki and its successors (Edinburgh, 2000 and Washington, 2002) and complied with the principles of Good Clinical Practice set by the International Conference on Harmonization and applicable German regulatory requirements. Written informed consent was obtained from patients at screening.

Male and female patients aged 18 years old or over were eligible to take part in the study if they were experiencing severe chronic pain, as assessed by the investigator, of mainly non-cancer origin (2.5% of patients had cancer-related pain) that required opioid treatment, or they were under current stable PR oxycodone therapy (40, 60 or 80 mg/day). Exclusion criteria included current alcohol or drug abuse, current acute pancreatitis, current severe cardiovascular or respiratory diseases (e.g., lung cancer or metastases), current severe renal or liver impairment (transaminase levels three times above normal range), liver or renal carcinoma or metastases. Patients were also excluded if they had a history of paralytic ileus, psychoses or Parkinson's disease, a known hypersensitivity to one of the study drugs or had participated in another clinical study within 30 days of study entry. Female patients of childbearing age without adequate contraception, or those who were pregnant or lactating, were excluded.

2.2. Procedures

The study had three phases: pre-randomisation (which consisted of screening and titration/run-in), a double-blind treatment period (maintenance phase), and an open-label phase (Fig. 1).

Following screening, patients entered either a titration or run-in period. Patients with inadequate pain control (indicated through a non-formal discussion between the investigator and patient), or those who were receiving an opioid other than oxycodone, entered a titration period and were individually titrated and stabilised at an oxycodone PR dose of 40, 60 or 80 mg/day. Patients on a stable oxycodone pretreatment dose of 40, 60 or 80 mg/day, with concomitant constipation (with or without laxative intake), entered
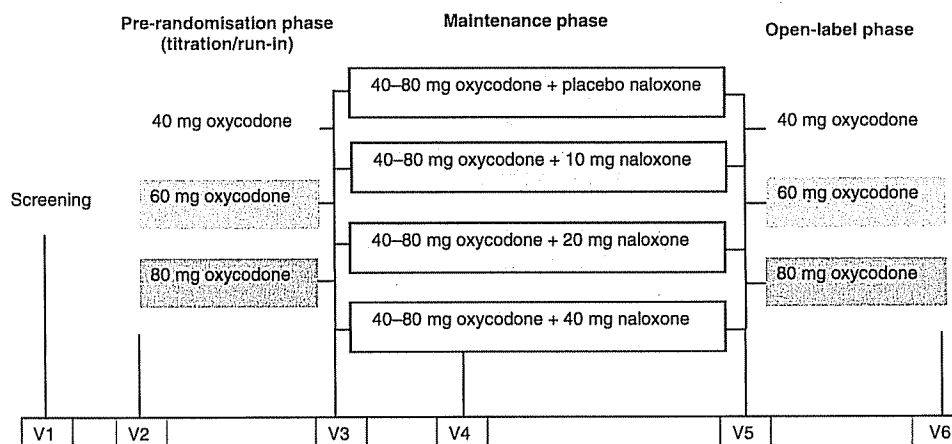

Fig. 1. Study design. The study consisted of three phases: pre-randomisation, maintenance and an open-label phase. Six study visits were planned (V1–V6) and assessments made at V3, 1 week into the maintenance phase (V4), V5 and V6.

a 7-day run-in period and were eligible for the maintenance phase without prior titration. For those patients who entered the titration phase, the starting dose of oxycodone was determined based on their previous analgesic.

At the end of the 2-week titration or the 7-day run-in period, patients were eligible to enter the double-blind treatment period (maintenance phase) if they were on a stable daily oxycodone dose of 40–80 mg for 7 consecutive days, received no more than five rescue medications per week (each defined as one 10 mg PR oxycodone tablet) and required laxatives to have at least three bowel evacuations per week. During the maintenance phase, rescue medication was restricted to a maximum of five intakes of 10 mg oxycodone per week.

Throughout the pre-randomisation phase, laxatives could be taken as needed. Patients were subsequently advised to stop laxative intake at the beginning of the maintenance phase; however, it could be restarted if no bowel evacuations occurred within 3 days of the start of the maintenance phase.

For the maintenance phase, patients were randomised to four study groups. The randomisation program balanced the relation between four naloxone dose groups (10, 20, 40 mg or placebo) in block sizes of four (1:1:1:1 randomisation). The dosing groups and ratios are shown in Table 1.

For each patient, the total study duration was up to 10 weeks, including the screening period, a minimum 2-week titration period (or a 1-week run-in period), a 4-week treatment period and an open-label phase of 2 weeks, when patients stopped taking naloxone but continued oxycodone therapy. In total, six visits (V1–V6) were planned and compulsory telephone contact was maintained every second day during titration/run-in, to assess pain control and make dose changes if necessary.

At screening, medical histories of patients were obtained. Standard physical examination and clinical laboratory evaluations were also conducted at screening and during the pre-randomisation and maintenance phases. These included haematology, blood chemistry and liver function tests, as well as urinalysis and measurement of glucose, total albumin, creatinine and uric acid levels.

The primary efficacy outcomes of interest were mean pain and mean bowel function. Pain was assessed subjectively using a numerical analogue scale (NAS) where 0 = no pain and 100 = worst imaginable pain. The NAS was completed twice daily by each patient (in their diary) in the morning, and in the evening 2 h after study medication intake. At screening and baseline (V2), pain was assessed by the investigator. At V3 (end of titration/run-in, start of maintenance), mean pain intensity was calculated from all values recorded during the last 7 days in the patient diary. Similar measurements were made at the end of the maintenance (V5) and open-label (V6) phases.

Mean bowel function was based on patients' subjective assessment during the last 7 days prior to each visit, and was calculated from the mean NAS of the three distinct components of the bowel function index (BFI) (Fig. 2). Higher scores indicate poor bowel function. Assessments were made at four different time points: V3, one week into maintenance (V4), V5 and V6.

Secondary efficacy outcomes associated with pain were daily pain intensity (mean of morning and evening measurements – calculated from NAS values in the patient diary) and amount of rescue medication (recorded daily in the patient diary). Those associated with bowel function included ease of defaecation (NAS), a feeling of incomplete bowel evacuation (NAS), patient judgment of constipation (NAS), stool frequency (patient diary) and laxative intake (study report entries; laxatives were identified by the WHO ATC code A06A).

Safety assessments, including physical examination, standard laboratory tests (as described above) and monitoring and recording of all adverse events were performed at each visit.

2.3. Statistical analysis

To test for non-inferiority regarding pain relief, one-sided t-tests of the absolute dose of naloxone versus placebo, with an equivalence limit of 8 on a NAS of 0–100 (defined as a clinically non-relevant difference), were conducted for mean pain during the last 7 days before the end of the maintenance phase visit (after 4 weeks of naloxone treatment). Two-sided 90% confidence intervals (CI) for the difference in means between the treatment groups were provided. In order to take imbalances in mean pain intensity at baseline into account, a post hoc ANCOVA analysis of the mean pain intensity with baseline value as covariate was conducted. For the analysis of the secondary endpoints, a Wilcoxon test was used to test for treatment differences for the absolute dose of naloxone.

To test for difference of absolute dose of naloxone versus placebo with respect to bowel function variables, t-tests were performed for the values obtained during the end of maintenance phase. In addition, two-sided 95% CIs for the difference in means between the treatment groups were provided. Summary statistics for the three components of mean bowel function were provided for each study visit for all analysis groupings. Wilcoxon tests of absolute dose of naloxone versus placebo were performed in the ITT population for mean values at V4 and V5.

Response surface analyses for pain intensity and bowel function were also performed for the end of the maintenance phase and displayed as response surface plots. The model included baseline values (mean during the last 7 days prior to randomisation) as a covariate, and oxycodone and naloxone doses as factors. The analysis was done twice: once with the stable oxycodone dose at the beginning of the maintenance phase (40 mg/day, 60 mg/day, 80 mg/day), and once with the oxycodone dose calculated as the mean of the total oxycodone doses per day (including rescue medication) during the last 7 days before the respective visit, during or at the end of the maintenance phase. The model-estimated responses were tabulated. The analysis was performed using the Statistical Analysis Software (SAS), Version 8.2.

The quadratic response surface model was used, as it provides not only results for all dose groups but also for the whole dose range, including doses in between. The values of all dose groups were included in the statistical model resulting in an extensive data pool, which leads to more precise information on the 2:1 dose ratio. This approach allows derivation of more information from

Table 1
Oxycodone and naloxone dose groups

	Group 1	Group 2	Group 3	Group 4
Naloxone daily dose (mg)	Placebo	10	20	40
Oxycodone daily dose (mg)	40, 60, 80	40, 60, 80	40, 60, 80	40, 60, 80
Oxycodone/naloxone dose ratio	40/Placebo	40/10, 4:1	40/20, 2:1	40/40, 1:1
	60/Placebo	60/10, 6:1	60/20, 3:1	60/40, 1.5:1
	80/Placebo	80/10, 8:1	80/20, 4:1	80/40, 2:1

Medication was taken in two doses (12-hourly) or divided by substance.

Bowel Function Index (BFI)

Please complete all items in this assessment.

1. Ease of defecation (NAS) during the last 7 days according to patient assessment:

0 = easy / no difficulty
100 = severe difficulty | | | |

Ask the subject: "During the last 7 days, how would you rate your ease of defecation on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?"

If the subject requires clarification, ask: "During the last 7 days, how easy or difficult was it to have a bowel movement on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?"

2. Feeling of incomplete bowel evacuation (NAS) during the last 7 days according to patient assessment:

0 = not at all
100 = very strong | | | |

Ask the subject: ""During the last 7 days, how would you rate any feeling of incomplete bowel evacuation on a scale from 0 to 100, where 0 = no feeling of incomplete evacuation and 100 = a very strong feeling of incomplete evacuation?"

If the subject requires clarification, ask: "During the last 7 days, how strongly did you feel that you did not empty your bowels completely? Please indicate how strong this feeling was on a scale from 0 to 100, where 0 = not at all and 100 = very strong"

3. Personal judgement of patient (NAS) regarding constipation during the last 7 days:

0 = not at all
100 = very strong | | | |

Ask the subject: "During the last 7 days, how would you rate your constipation on a scale from 0 to 100, where 0 = not at all and 100 = very strong"

If the subject requires clarification, ask: "During the last 7 days, how would you rate how constipated you felt on a scale from 0 to 100, where 0 = not at all and 100 = very strong"

Fig. 2. The bowel function index (BFI) is a three-item questionnaire to measure constipation from the patient's perspective. Instructions for administering each item of the BFI are indicated in the grey sections below each item. Subjects are asked each item in the BFI in the form of a question. If the subject does not understand what the question is asking, clarification may be provided by restating the question as indicated in the grey section. The subject's response to each question is written in the space provided. Study personnel confirm each answer provided by the subject by signing the review box below each question. To avoid any form of response bias, study personnel must not lead the subjects in their answers (e.g., study personnel should not provide examples of answers to a given question).

the available data and to draw more meaningful conclusions on the efficacy of the investigated medicinal product.

For the safety analysis, all continuous variables were summarised using descriptive statistics. Adverse events were summarised by the absolute number and percentage of patients on a system organ class and preferred term level (MedDRA). In addition, the number of patients and the number of adverse event occurrences were provided by seriousness, severity and relationship.

3. Results

From the participating 28 centres, a total of 230 patients were screened; 202 were subsequently randomised and treated, and 166 completed the study (Fig. 3). A centre effect could not be observed, as assessed by a post hoc mixed model analysis. All randomised patients received study medication and were included in the safety population. For the per-protocol and safety analyses, only non-missing values were taken into account. An intent-to-treat (ITT) analysis was performed for all efficacy endpoints. The ITT population was defined as all randomised patients who received at least one dose of naloxone or corresponding naloxone placebo and had at least one efficacy assessment, and consisted of 196 (97.0%) patients. Six patients were excluded from the ITT population but included in the safety population for analysis of safety endpoints. Of these, five patients were excluded due to missing post-baseline efficacy assessments, and one patient received two different naloxone doses during the course of the study. For

the analyses of the efficacy and safety results, different approaches were taken. For analgesic efficacy, the aim was to demonstrate non-inferiority of the oxycodone/naloxone combination against oxycodone alone; per-protocol (PP) data were used, as they are more conservative than ITT data. Conversely, for the bowel function analysis, as the aim was to demonstrate superiority of the oxycodone/naloxone combination over oxycodone alone, ITT data were used.

All treatment groups and dose ratio groups were generally well balanced regarding demographic and baseline characteristics (Table 2). No clinically relevant differences between the treatment groups or dose ratios concerning prior or concomitant medications were noted. Back pain was the most common pain-causing disease (24.3%), followed by post-operative complications (15.3%).

No significant differences in the intensity of mean pain between the treatment groups (absolute naloxone groups; Fig. 4) were observed at any of the study time points. Fig. 4 also shows that the mean pain score declined from the pre-randomisation phase (titration/run-in) to randomisation (start of maintenance). Additionally, the level of analgesia in patients during the switch from the PR oxycodone/naloxone combination back to oxycodone alone also remained stable.

The differences between naloxone placebo treatment and the 10 mg, 20 mg and 40 mg naloxone treatments were small, with the 90% CIs for the differences being narrow relative to the 0–100 pain scale. The 90% CIs for the differences based on an ANCOVA test with V3 pain as covariate were similarly narrow: −2.0
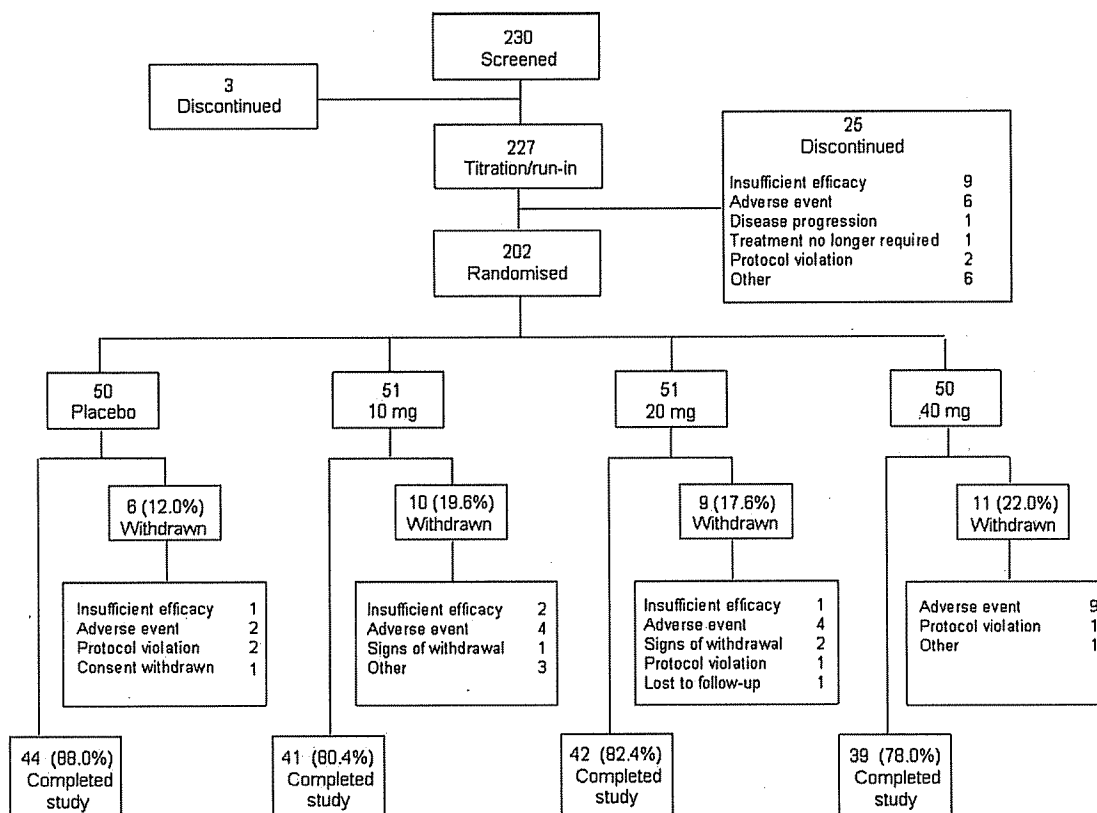
Fig. 3. Patient disposition. Of the 230 patients screened for the study, 202 were randomised for treatment and 166 completed the study. Reasons for discontinuation are shown.

Table 2
Patient demographics and baseline characteristics

Characteristic	Absolute dose of naloxone				
	Placebo (n = 50)	Naloxone 10 mg (n = 51)	Naloxone 20 mg (n = 51)	Naloxone 40 mg (n = 50)	Total (n = 202)
Sex, n (%)					
Male	19 (38.0)	18 (35.3)	17 (33.3)	21 (42.0)	75 (37.1)
Female	31 (62.0)	33 (64.7)	34 (66.7)	29 (58.0)	127 (62.9)
Mean age (years)	53.8	58.4	56.0	57.0	56.3
Pain-causing disease, n (%)					
Back pain	11 (22.0)	16 (31.4)	14 (27.5)	8 (16.0)	49 (24.3)
Fibromyalgia	3 (6.0)	5 (9.8)	2 (3.9)	5 (10.0)	15 (7.4)
Intervertebral disc herniation	6 (12.0)	3 (5.9)	2 (3.9)	3 (6.0)	14 (6.9)
Neck pain	2 (4.0)	2 (3.9)	3 (5.9)	1 (2.0)	8 (4.0)
Neuropathic pain	2 (4.0)	2 (3.9)	0 (0.0)	3 (6.0)	7 (3.5)
Pain	3 (6.0)	3 (5.9)	2 (3.9)	3 (6.0)	11 (5.4)
Post-operative complications	11 (22.0)	6 (11.8)	5 (9.8)	9 (18.0)	31 (15.3)
Sciatica	0 (0.0)	2 (3.9)	4 (7.8)	2 (4.0)	8 (4.0)
Spinal stenosis	1 (2.0)	4 (7.8)	4 (7.8)	2 (4.0)	11 (5.4)
Tumor patients	1 (2.0)	1 (2.0)	1 (2.0)	2 (4.0)	5 (2.5)
Mean duration of pain (months)	149.3	113.1	154.7	136.7	138.6

to 8.2, −6.7 to 4.0 and −3.3 to 7.4 for 10 mg, 20 mg and 40 mg naloxone, respectively, versus placebo. The differences in the intensity of mean pain between the dose ratio groups were also very small (data not shown); however, given the small patient populations in each group, a statistical analysis was not conducted.

Results obtained in the per-protocol population were generally mirrored by those of the ITT population for the analysis of intensity of mean pain. Overall, the results indicate that the addition of naloxone did not reduce the analgesic efficacy of oxycodone.

The other primary efficacy outcome in this study was bowel function. Scores obtained from the BFI decreased as the naloxone dose increased (Fig. 5). At V4, the difference between 40 mg naloxone and placebo was statistically significant ($p = 0.004$), while at the end of maintenance (V5) the differences for both the 20 mg and 40 mg doses of naloxone and placebo were statistically significant ($p < 0.05$). According to the analysis by dose ratio, at the end of the maintenance phase (V5), mean (±SD) bowel function score was lowest in the 1:1, 1.5:1 and 2:1 dose ratios: 21.9 (±22.25), 21.8 (±21.35) and 26.7 (±23.98), respectively.
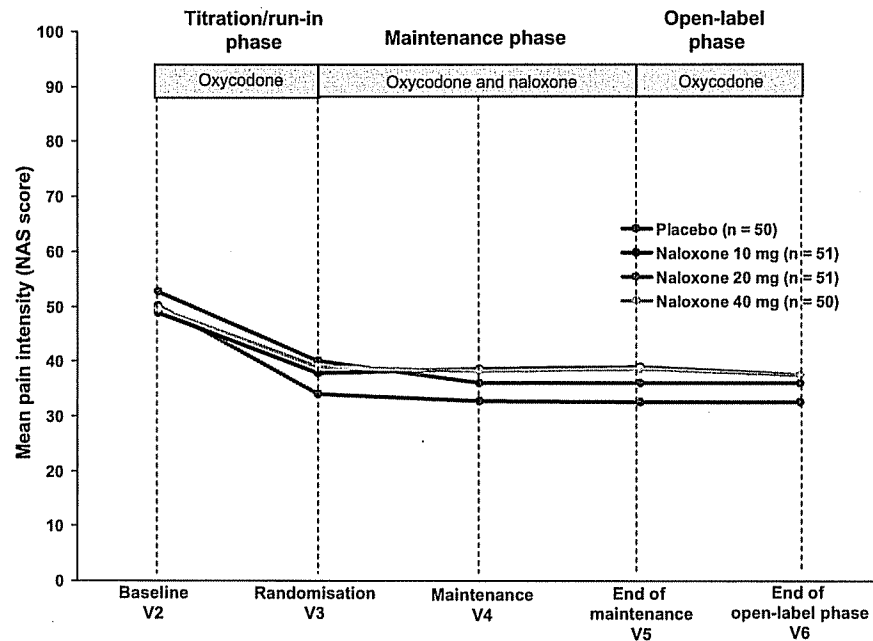
Fig. 4. Mean pain intensity at each study visit by absolute naloxone dose (per-protocol population) (NAS score: 0 = no pain, 100 = worst imaginable pain). There were no significant differences in mean pain intensity between the treatment groups at any of the study visits.
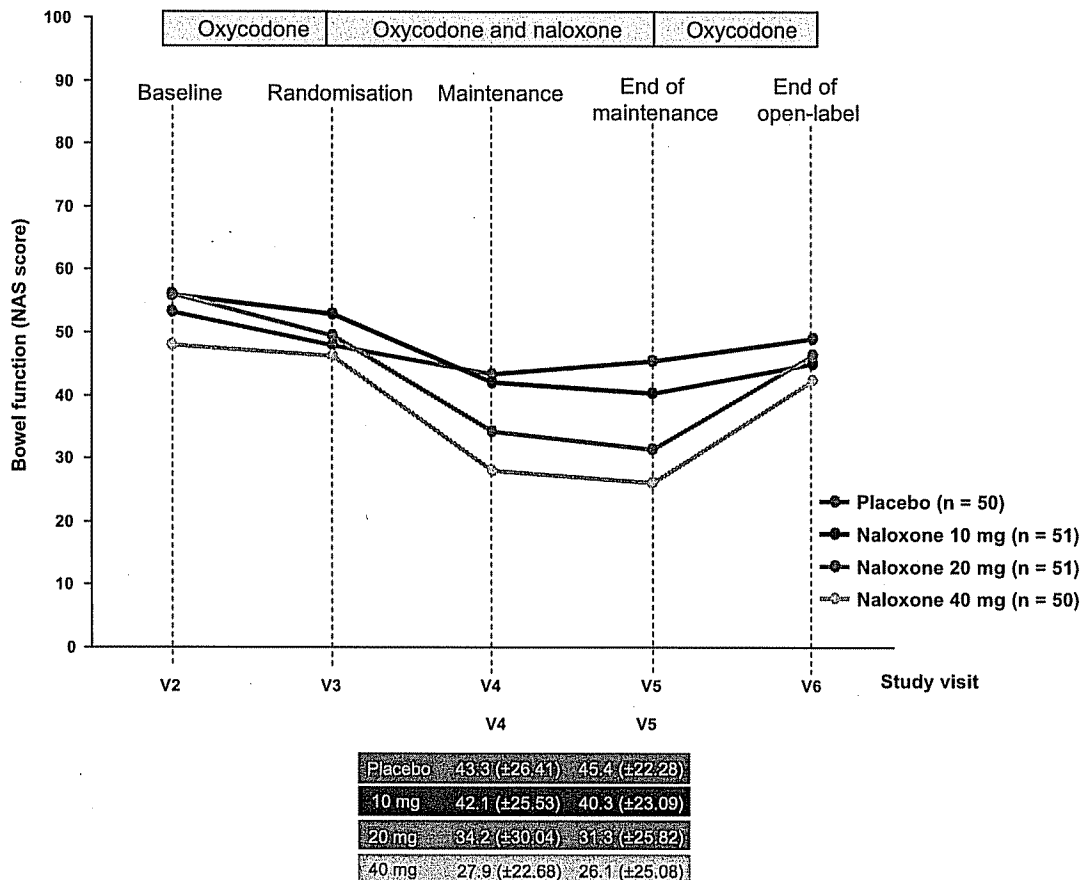

	V4	V5
Placebo	43.3 (±26.41)	45.4 (±22.28)
10 mg	42.1 (±25.53)	40.3 (±23.09)
20 mg	34.2 (±30.04)	31.3 (±25.82)
40 mg	27.9 (±22.68)	26.1 (±25.08)

Fig. 5. Mean bowel function at each study visit (ITT population) as measured using the bowel function index (BFI). Increasing scores reflect increasing severity of bowel dysfunction. At Visit 4 there was a significant improvement in bowel function for the 40 mg naloxone group compared with placebo (p = 0.004). Both the 20 mg and 40 mg naloxone dose groups showed significant improvements in bowel function compared with placebo at Visit 5 (p < 0.05).

The removal of naloxone from the treatment regimen at the end of the maintenance phase resulted in an increase in the BFI score, indicating a worsening of bowel dysfunction. At the end of the open-label phase (V6), BFI scores had almost returned to baseline values (Fig. 5).

The post hoc analysis confirmed the original statistical analysis. The analysis of model-estimated responses also showed that bowel function remains relatively constant within the oxycodone/naloxone dose ratio, but decreases as the amount of naloxone decreases, within the same absolute oxycodone dose. This was confirmed by the surface plot for bowel function versus daily naloxone and oxycodone doses (Fig. 6).

Overall treatment effect estimates were obtained for specific ratios. The estimates were calculated by combining the results from the different oxycodone/naloxone combinations; for example, the 2:1 ratio estimate was formed by averaging the predicted results of the 40/20 mg, 60/30 mg, and 80/40 mg oxycodone/naloxone combinations, relative to naloxone placebo. The estimated mean differences (SE) in mean bowel function for various oxycodone/naloxone ratios versus naloxone placebo groups are shown in Table 3. The estimates indicate that bowel function improves progressively as the oxycodone/naloxone ratio decreases, with the estimated improvement at 2:1 approximately 50% higher than at 4:1 ($p < 0.05$) and with a minimal improvement from the 2:1 ratio to the 1.5:1 ratio.

The main secondary efficacy outcome for the pain component of the study was daily pain intensity. This was shown to be stable for all treatment groups throughout the course of the maintenance phase. The demand for rescue medication also remained stable throughout the study period. No identifiable trend was observed in the numbers of patients taking rescue medication across all treatment groups.

Secondary efficacy outcomes for the bowel function component were the individual components of the BFI, stool frequency and laxative intake.

Table 3
Response surface analysis of bowel function efficacy (BFI) by oxycodone/naloxone ratio: estimated improvement (SE)/difference versus naloxone placebo at V5

Oxycodone/naloxone ratio	Overall improvement (SE) versus placebo
6:1	8.0 (3.3)
4:1	11.0 (4.1)
3:1	13.4 (4.6)
2:1	16.2 (4.5)
1.5:1	16.5 (5.1)

For each treatment group there was an increase in stool frequency (per day), with increasing doses of naloxone during the last 7 days before V4; the mean (±SD) values were 0.9 (±0.46), 1.0 (±0.48), 1.2 (±0.82), 1.4 (±0.63) for placebo, 10 mg, 20 mg and 40 mg, respectively ($p < 0.001$ for 40 mg versus placebo). A similar pattern was also observed at V5, the mean (±SD) values being 0.9 (±0.46), 1.0 (±0.48), 1.0 (±0.45), 1.1 (±0.59) for placebo, 10 mg, 20 mg and 40 mg, respectively, with a statistically significant difference to placebo ($p < 0.05$) obtained for 40 mg naloxone. The mean (±SD) number of days with laxative intake during the last 7 days of the maintenance phase decreased with increasing absolute dose of naloxone: 3.9 (±3.38), 2.6 (±3.34), 2.0 (±3.14), 1.6 (±2.93) for placebo, 10 mg, 20 mg and 40 mg naloxone, respectively ($p < 0.001$ for all doses of naloxone versus placebo). The number of patients taking laxatives within that timeframe was 35 (81%), 26 (70%), 18 (45%), 21 (58%) for placebo, 10 mg, 20 mg and 40 mg naloxone, respectively.

A total of 202 patients were included in the safety analysis. No trends or possible treatment-related pathological laboratory findings could be identified for any of the treatment groups. No deaths occurred during the study.

During the maintenance phase, the incidence of adverse events was comparable across all treatment groups (range 62.7–70.0%), although the number of events increased with increasing naloxone
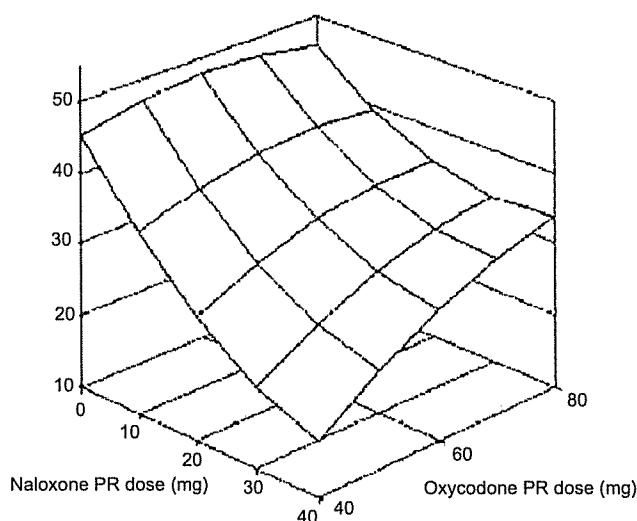
Oxycodone PR/naloxone PR dose ratio	40 mg/ placebo	60 mg/ placebo	80 mg/ placebo	1/1	1.5/:1	2/1	3/1	4/1	6/1	8/1
n	17	17	16	15	17	32	17	32	11	22

Fig. 6. Response surface plot (ITT population) of mean bowel function at V5 (end of the maintenance phase) versus daily naloxone and oxycodone doses shows that bowel function remains relatively constant within the oxycodone/naloxone dose ratio, but decreases as the amount of naloxone decreases, within the same absolute oxycodone dose.

Table 4
Overall summary of adverse events by absolute naloxone dose during the maintenance phase

	Naloxone placebo		10 mg Naloxone		20 mg Naloxone		40 mg Naloxone	
	Patients	Events	Patients	Events	Patients	Events	Patients	Events
	n = 50 (100%)	n	n = 51 (100%)	n	n = 51 (100%)	n	n = 50 (100%)	n
Number (%) of patients with at least one adverse event	32 (64.0%)	111	35 (68.6%)	119	32 (62.7%)	129	35 (70.0%)	140
Mild	23 (46.0%)	76	23 (45.1%)	62	22 (43.1%)	65	24 (48.0%)	64
Moderate	13 (26.0%)	32	17 (33.3%)	40	19 (37.3%)	42	21 (42.0%)	52
Severe	2 (4.0%)	3	8 (15.7%)	17	8 (15.7%)	22	11 (22.0%)	24

dose – 111, 119, 129 and 140 events for the placebo, 10 mg, 20 mg and 40 mg naloxone doses, respectively. No relationship to dose ratio was identified. Most adverse events were mild or moderate in intensity. There was a slight trend for an increase in moderate and severe adverse events with increasing naloxone dose (Table 4), but the incidence of serious adverse events was low and generally comparable across all active naloxone treatment groups.

The only difference in the incidence of adverse events between dose ratio treatment groups was the incidence of diarrhoea – this was 50% in the 1.5:1 dose ratio group, but substantially less (29.4%), in the 2:1 dose ratio group. The incidence of diarrhoea was higher among patients taking active naloxone and increased with higher doses; 12.0%, 19.6%, 23.5% and 36.0% for placebo, 10 mg, 20 mg and 40 mg naloxone groups, respectively.

Overall, the frequency of discontinuations due to adverse events during the maintenance phase increased with an increasing dose of naloxone; 2.0%, 9.8%, 11.8% and 18.0% for the placebo, 10 mg, 20 mg and 40 mg naloxone groups, respectively. The main reason for discontinuation in the naloxone 20 mg and 40 mg treatment groups was related to diarrhoea: 0.0%, 2.0%, 7.8% and 12.0% patients discontinued in the placebo, 10 mg, 20 mg and 40 mg naloxone treatment groups, respectively. Study discontinuation due to diarrhoea was related to its severity or the degree of discomfort caused in patients, not duration. In patients who did not withdraw from the study, diarrhoea as a side effect was transient.

4. Discussion

Results from this clinical trial indicate that the analgesia provided by PR oxycodone co-administered with PR naloxone is comparable to that of PR oxycodone administered alone, and significantly reduces the impact of opioid-induced constipation. During the maintenance phase, the addition of naloxone did not lead to the worsening of pain – no apparent differences in the intensity of daily pain were observed between any of the treatment groups, indicating that there was no interference of naloxone with the analgesic effect of oxycodone. Analysed by absolute naloxone dose, mean pain scores with naloxone were equivalent to placebo. The lack of effect of naloxone on the analgesic efficacy of oxycodone is further demonstrated by the observation that the demand for rescue medication in all treatment groups remained stable throughout the study period.

At V5 (end of the maintenance phase) mean bowel function scores were the lowest for all treatment groups, indicating that the addition of PR naloxone to the PR oxycodone regimen of patients significantly reduced the severity of bowel dysfunction. This improvement in bowel function was dose dependent – the severity of opioid-induced constipation was reduced progressively as the oxycodone/naloxone ratio decreased. The small improvement observed in the naloxone placebo group was negligible. Overall, the dose-dependent improvement in bowel function indicates a naloxone-specific effect. As expected, analysis of the secondary endpoints revealed similar findings to the primary endpoint – improvements in the individual measurements of bowel dysfunc-

tion (ease of defaecation, feeling of incomplete bowel evacuation and judgment of constipation) were noted, with the greatest improvements seen at dose ratios of 1:1, 1.5:1 and 2:1 or an absolute naloxone dose of 40 mg. Stool frequency also increased with an increase in naloxone dose, while the use of laxatives decreased. All improvements decreased after termination of the maintenance phase, indicating that continuous naloxone treatment might be necessary in order to maintain normal bowel function.

Modelled estimates of overall treatment effect for specific ratios indicated that the estimated improvement at 2:1 was approximately 50% higher than at 4:1 ($p < 0.05$). However, there was only minimal improvement from the 2:1 ratio to the 1.5:1 ratio – this indicates that improvement in bowel function may reach a plateau, which can be achieved with the 2:1 ratio. Based on the analysis of the efficacy and safety results by dose and dose ratio, the 2:1 ratio with a 40 mg maximum daily dose of naloxone was deemed optimal with regard to efficacy and tolerability and best suited for further evaluation. The mean (±SD) number of days with laxative intake during the last 7 days of the maintenance phase decreased with increasing absolute dose of naloxone: 3.9 (±3.38), 2.6 (±3.34), 2.0 (±3.14), 1.6 (±2.93) for placebo, 10 mg, 20 mg and 40 mg naloxone, respectively. Still, laxatives were used even with the highest naloxone dose. Naloxone can only reduce or prevent opioid-induced constipation. Laxatives may still be needed to alleviate constipation caused by other medication or idiopathic constipation.

The safety profile of oxycodone and naloxone are well established. Nausea, vomiting and sedation are typical opioid-related adverse events, while abdominal pain, cramping and diarrhoea are typically associated with naloxone use. Both agents, when co-administered during the maintenance phase of this trial were well tolerated – adverse events, beyond the nature and severity of those expected, were not reported. The safety profiles of all treatment arms were comparable; the only exception with regard to adverse events was diarrhoea, which increased with increasing naloxone dose. However, this side effect was transient in the majority of patients who suffered from it, and might be considered as an 'overshoot' effect.

The use of immediate-release oral naloxone has been previously studied to ascertain its effect in reducing opioid-induced constipation; however, the study populations have been small and the results equivocal (Sykes, 1996; Meissner et al., 2000; Liu and Wittbrodt, 2002; Latasch et al., 1997). In some of these trials, withdrawal symptoms were observed even at low doses of oral naloxone. In the current trial PR naloxone was used. The slow release of naloxone might reduce the risk of overburdening the hepatic enzymatic systems responsible for its metabolism, thereby reducing the risk of systemic antagonism. The results provide strong evidence that the addition of PR oral naloxone to an opioid-based analgesic regimen does not reduce the efficacy of the opioid. The negative impact of opioid-induced constipation is often overlooked and under-appreciated; it is one of the most common reasons patients avoid or abandon opioid use and, consequently, suffer from pain needlessly (Thorpe, 2001). Furthermore, if opioid-induced constipation is not addressed adequately, it can, in itself

become a cause of pain, thus increasing opioid use and generating a positive feedback loop (Tamayo and Diaz-Zuluaga, 2004).

Further studies investigating the efficacy and safety of the combination are ongoing. In addition, mucosal lesions, gastric emptying and regurgitation are interesting endpoints in opioid-induced bowel dysfunction that could be included in future studies.

A combination of the strong opioid oxycodone with naloxone in a PR formulation could allow patients suffering from chronic pain to receive adequate analgesia on a long-term basis and to maintain normal bowel function.

An oxycodone/naloxone combination will also be of great benefit to healthcare professionals who are responsible for the care of patients with severe chronic pain. With the reduced incidence of opioid-induced constipation and subsequent need for laxatives, or sometimes even more severe interventions such as enemas and manual evacuations, the management of patients can be improved. The availability of a strong opioid with an improved tolerability profile, such as a fixed 2:1 oxycodone/naloxone combination, has significant added therapeutic value, thus representing a major advance in the treatment and quality of life of patients suffering from severe chronic pain.

Acknowledgements

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